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RESEARCH ARTICLE

A CASE REPORT: EXPLORING STARGARDT DISEASE - CLINICAL FEATURES AND GENETIC INSIGHTS

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Abstract

Stargardt disease (SD) stands as a prominent inherited macular dystrophy affecting both adults and children, characterized by bilateral and symmetrical maculopathy with autosomal recessive transmission linked to the ABCA4 gene. We aim to present a comprehensive exploration of SD, delving into its clinical manifestations, genetic intricacies, and potential therapeutic interventions. This case report highlights a 46-year-old north African male with late-onset STGD with gradual bilateral vision decline, central macular atrophy, and yellow deposits in the perimacular region. the spectrum of SD is diverse, ranging from childhood onset to adult manifestation, often mimicking age-related maculopathy. Stargardt disease's genetic landscape is intricately governed by the ABCA4 gene, marked by over 900 variants across its 50 exons. This genetic diversity extends to dominant genes such as STGD4, ELOVL4, and PRPH2, contributing to a spectrum of retinal disorders. Therapeutic approaches for Stargardt disease involve drugs targeting the visual cycle, a modified vitamin A, and ongoing gene replacement and stem cell therapy trials This comprehensive review amalgamates clinical observations, genetic considerations, and emerging therapeutic avenues.

Introduction:-

Stargardt disease (SD) is one of the most common inherited macular dystrophy in both adults and children.

It is a bilateral and symmetrical Maculopathy with recessive autosomal transmission linked to the ABCA4 gene, located on chromosome 1 in the region 1p22. It is both clinically and genetically highly heterogeneous.

Age of onset is a surrogate marker: The earlier the onset, the more severe the disease course, with better prognosis generally associated with a later onset.

There is slow progressive loss of retinal function and structure over time; however, there is marked variability both within and between families, suggesting that other important factors influence phenotype, including genetic modifiers and the environment.

Herein, we report a case of late-onset SD, discuss clinical features and review the role of genetics in SD.

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Case Report:
We report the case of 46 years old north africanman, with a family history macular degeneration in his father and unprecised retinal dystrophy in his older brother, the family history did not mention consanguinity; who presents gradual and bilateral decline in vision in both eyes for over two years.

Best Vision acuity was counting fingers in ODG. Anterior segment examination was unremarkable. IOP was 13 mmHg OD and 15 mmHg OS. Dilated fundus examination revealed Central macular astrophy with yellow deposits in the perimacular region. This feature of the fundus was bilateral and symmetrical. The autofluorescence showed the presence of an oval-shaped hypoautofluorescent area with well-defined borders in the macular region. Fluorescein angiography showeda central hyperfluorescence and choroidal silence, corresponding to delayed fluorescein diffusion at the choroidal level. Optical coherence tomography revealed bilateral macular atrophy. Full-field electroretinogram revealed cone and rod dysfunction. Genetic testing by target enrichment and next-generation sequencing was performed and revealed two pathogenic variations in the ABCA4 gene, c.5461-10T>C4 and c.5603A>T,5 confirming the diagnosis of late-onset SD.

Discussion:-

Stargardt's disease, initially described by Karl Stargardt in 1909, is the most prevalent macular degeneration in children below 15 years old. This genetic disorder leads to a progressive and irreversible central vision loss, typically commencing between the ages of 7 and 15. While it commonly manifests in youth, Stargardt's disease can also mimic age-related maculopathy, causing diagnostic challenges in adults (1-7).

The condition, with no gender or race predilection, exhibits considerable variability in onset age, visual impairment, clinical presentation, and severity. It follows autosomal recessive inheritance linked to mutations in the ABCA4 gene. (ATP-binding cassette transporter gene).

Patients with Stargardt's disease experience bilateral central visual loss, dyschromatopsia, central scotoma, and slow dark adaptation. paradoxally, fundus examination might appear normal initially despite visual complaints, later progressing to pigment mottling, a “beaten bronze” appearance of the macula, macular atrophy, fundus flecks or even bull’s eye maculopathy may arise. Flecks are typically “pisciform,” round, amorphous, or dotlike yellow-white lesions. Their distribution may change with time. The number of flecks does not have a good correlation with the visual loss.

While commonly associated with a younger demographic, Stargardt's disease can present later in adulthood, mimicking conditions like age-related macular degeneration (12-15). Autofluorescence is the key examination for diagnosis, revealing flavimaculatus lesions distinctly. Fluorescein angiography will exhibit choroidal silence called Bonin.

Stargardt's disease differs from fundus flavimaculatus, presenting a more severe phenotype with earlier onset and faster visual decline. Optical coherence tomography reveals early damage to the ellipsoid lineline in the perifoveal macular zone and atrophic macular remodeling with a decrease in the photoreceptor layer. (16).

The global electroretinogram is generally normal (Stargardt disease type 1), but alterations in scotopic (type 2) or photopic (type 3) responses may indicate a risk of peripheral damage. Prognosis becomes unfavorable when visual acuity drops below 6/10.

Differential diagnosis includes age-related macular degeneration, PRPH2 gene-associated pattern dystrophy, mitochondrial retinal dystrophy associated with maternally inherited diabetes and deafness (MIDD), and pentosan polysulfate toxic maculopathy. (17, 18)

A number of features can be used to differentiate SD of later onset from these other conditions. The drusen of AMD tend to be round and not pisciform, more centered in the macula, less symmetric between the eyes, and less intensely hyperautofluorescent. And also Angiographic findings of a dark choroid, while common in SD, would not be expected in the other aforementioned diseases.

• SD and other ABCA4-related ocular disorders :

STGD1 is inherited in an autosomal recessive fashion and is caused by sequence variants in the gene ABCA4, with the carrier frequency believed to be up to 1 in 20. (19) This gene codes for a protein located on the disc of the external segments of the cones and the rods which allows the passage of retinoids (derived from vitamin A) through the cell membranes after photoexcitation of rhodopsin. The loss of function of the protein leads to an accumulation of these derivatives and thus the destruction of photoreceptors.This gene is active only in the retina. Several mutations of this gene can be the cause of the disease. (20)

This same ABCA4 is a large, highly polymorphic gene, consisting of 50 exons, with over 900 disease-associated variants reported to date . Some of the retinal diseases that are caused by it are : retinitis pigmentosa ,Cone and rod dystrophy, adult Stargardt dystrophy. Therefore, the frequency of all diseases related to ABCA4 gene abnormalities increases to 1 in 10,000. (21-23)

The genetics is extremely heterogenous and may be responsible for wide variations in clinical presentations. Mild reduction in ABCA4 activity results in about 95% of cases of STGD; moderate loss of activity results in cone-rod dystrophy (about 30–50% of cases); and complete loss results in retinitis pigmentosa (RP) with complete loss of rod and cone function (about 8% of cases of autosomal recessive RP). (24)

• Others mutations correled to SD :

Other mutations, accounting for the remaining 5% of STGD cases, are in the dominant genes STGD4 and ELOVL4 and PRPH2. The ELOVL4 protein plays a role in making a group of fats called very long-chain fatty acids. Mutations in the ELOVL4 gene lead to the formation of ELOVL4 protein clumps in the cells, interfering with their activity and eventually leading to cell death. (24)

• Therapeutic Strategies: From Visual Cycle to Gene Replacement

Numerous drugs, targeting diverse aspects of the visual cycle, present potential benefits in slowing STGD1 progression. Strategies involve reducing toxic by-products, inhibiting enzymes in the visual cycle, and directly targeting metabolites like A2E (25). A chemically modified vitamin A aims to preserve normal visual cycle function while preventing harmful metabolite formation (26-28). Gene replacement therapy, utilizing adeno-associated virus (AAV) vectors, faces challenges due to the larger size of ABCA4. A lentiviral vector, with a larger cargo capacity, is in an ongoing phase I/II clinical trial (29-32).

• Stem Cell Therapy: A Glimpse into Future Interventions

Considering the progression sequence in STGD1, dysfunction/loss of retinal pigment epithelium (RPE) cells precedes photoreceptor cell loss. RPE cells, relatively easy to generate in the laboratory, emerge as potential candidates for Phase I/II stem cell therapy trials using human embryonic stem cells (33). The future of STGD1 management holds promise in diverse therapeutic avenues.

Conclusion:-

Stargardt disease, a hereditary bilateral central degeneration, typically symmetrical, it emerges between ages 6 and 15, with later-onset cases. As a major cause of certifiable blindness.

Recent advances for early identification include distinctive clinical features and precise genetic testing allowing better-informed advice on prognosis. While ongoing trials show promise, no curative treatment exists, underscoring the crucial role of early diagnosis in mitigating severe visual acuity loss. Psychological support is paramount at diagnosis for both patients and families.

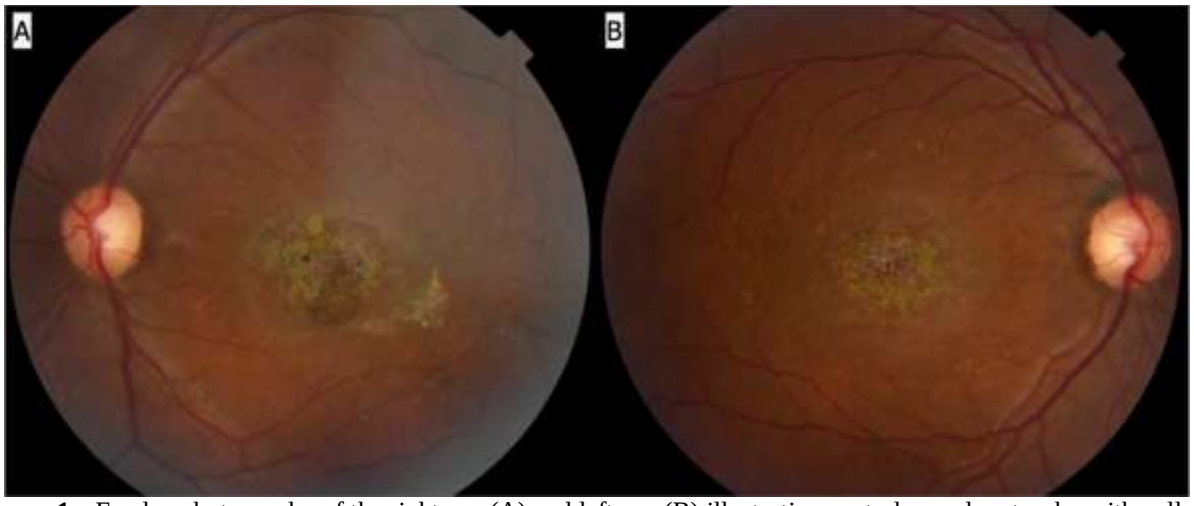

Figure 1:- Fundus photography of the right eye (A) and left eye (B) illustrating central macular atrophy with yellow deposits in the perimacular region.

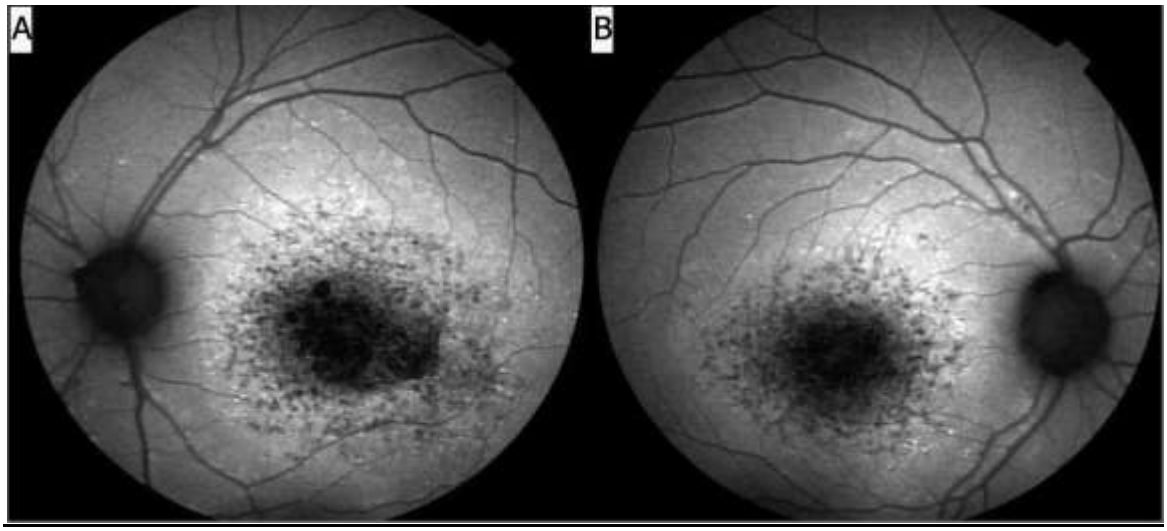

Figure 2:- Autofluroescence of the right eye (A) and left eye (B) portraying oval-shaped hypoautofluorescent area.

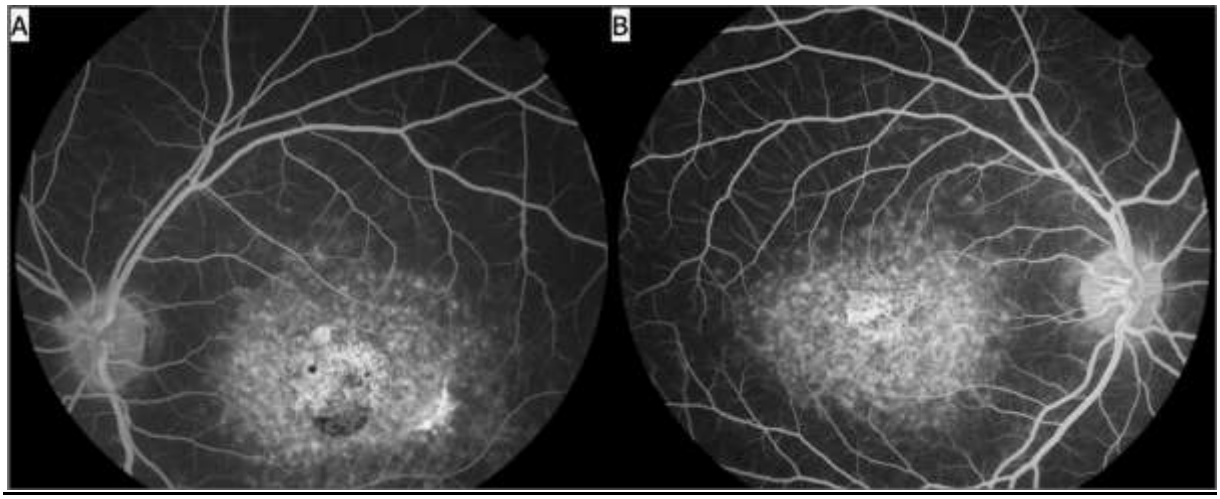

Figure 3:- Fluorescein angiography of the right eye (A) and left eye (B) showing central hyperfluorescence and choroidal silence.

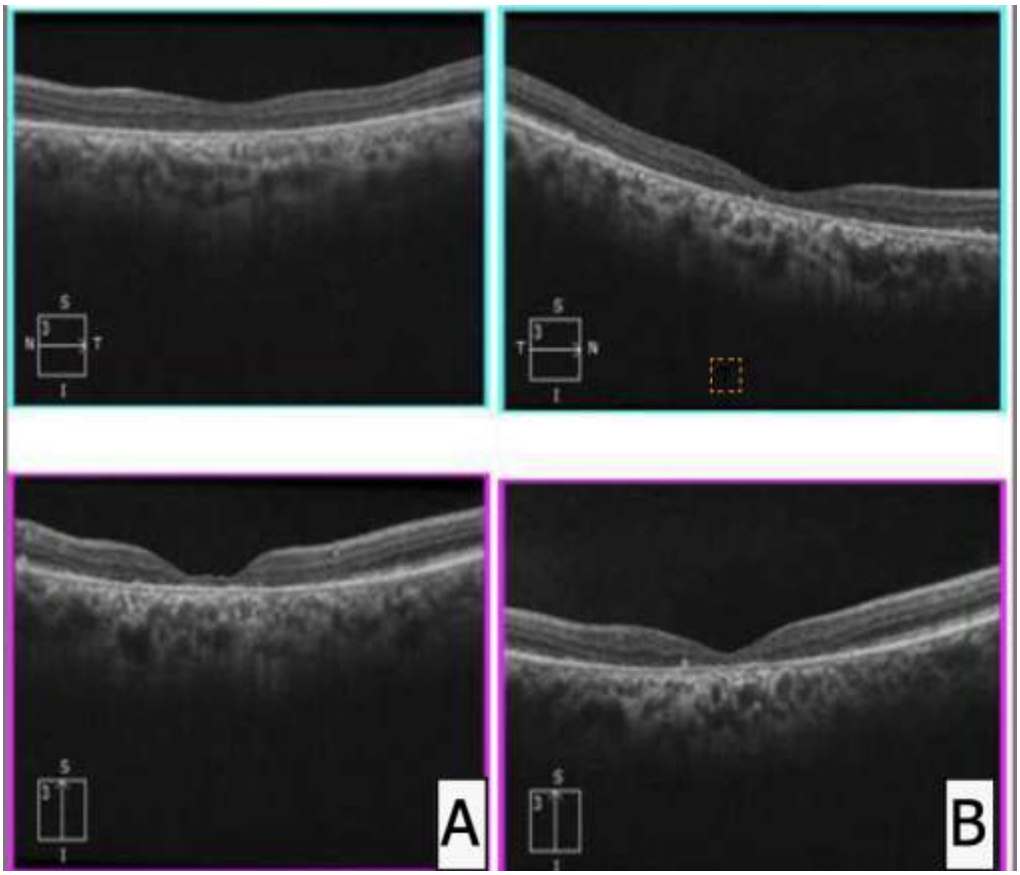

Figure 4:- Horizontal and vertical OCT B-scans of the right eye (A) and left eye (B) showing bilateral macular atrophy.

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